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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/076,306	02/12/2002	Jan Urban Kristoffer Hellstrand	MAXIM.026C3	1217

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 11/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/076,306	HELLSTRAND ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 1-16 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 1-16 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 1/7/05+2/12/02.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Please note that the examiner assignment has changed.

Sections of Title 35, U.S.Code, not found in this action can be found in a prior action.

Claim 10 has been canceled. Claims 1 and 8 have been amended. Claims 1-9 and 11-16 are pending and under consideration.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear how claim 9 further limits claim 8. Claim 8 requires the administration of the hydrogen peroxide scavenger which is catalase, superoxide dismutase or glutathione peroxidase. Claim 9 recites "wherein the hydrogen peroxide scavenger catalyses the decomposition of hydrogen peroxide". It is a chemical characteristic of catalase, superoxide dismutase or glutathione peroxidase that reaction with hydrogen peroxide results in the decomposition of hydrogen peroxide. None of catalase, superoxide dismutase or glutathione peroxidase have any other mechanism for "scavenging" hydrogen peroxide other than reaction with hydrogen peroxide resulting in decomposition of to water and oxygen.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-16 are methods dependent upon the identity of an "NK activating cytokine" and an "NK activating flavonoid". The claims are thus dependent upon a genus of cyokines or a genus of flavonoids, both of which activate NK cells. The specification describes Il-1, Il-2, Il-12, IFN-alpha, beta and gamma as cyokines which activate NK cells. However there is no nexus between any of Il-1, Il-2, Il-12 in terms of amino acid sequence or receptor binding because each

of these interleukins binds to a different receptor and thus has different physiological consequences. It is noted that Hellstrand et al (WO 91/04037) teach that the NK augmenting effect of Il-2 is attributed to the Il-2 receptor on NK cells (page 4, lines 30-32). There is also no nexus between any of Il-1, Il-2, Il-12 and the interferons IFN alpha, beta or gamma because the individual proteins have no common structural attribute and interact with different cellular proteins. Thus, the disclosure of any of Il-1, 2, 12 or IFN-alpha, beta or gamma cannot adequately describe the genus of "NK cell activating cytokines" because there is no nexus between the structure of those proteins already recognized in the art and the interaction between a particular cellular structure. Further, when given the broadest reasonable interpretation, the claim encompasses cytokines which indirectly activate NK cells, and these indirect activators need not have any similarity to the disclosed Il-1, Il-2, Il-12, IFN-alpha, beta and gamma. The same analysis applies to NK activating flavonoids. The specification describes flavone-8- acetic acid and xanthenone acetic acid as NK cell activators. The structural genus encompassed by the term "flavonoid" is very large encompassing Anthocyanins, Proanthocyanidins, Benzoflavones, Biflavonoids, Catechin, Chalcones, Flavanones, Flavones, Flavonolignans, Flavonols and Isoflavones. The disclosure of flavone-8- acetic acid and xanthenone acetic acid cannot adequately describe the claimed genus of NK activating flavonoids because the genus encompasses molecules which are highly variant from that of flavone-8- acetic acid and xanthenone acetic acid. One of skill in the art would reasonable conclude that applicant was not in possession of the genuses of NK activating cytokines or flavonoids.

Claims 8, 9 and 11 rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Tatsuo (JP 59059628) or the abstract of Tatsuo (JP 59059627).

Claim 8 is drawn in part to a method of inhibiting tumor growth in a subject suffering from neoplastic disease comprising administering to a subject with a neoplastic disease in need thereof an effective amount of a NK-cell activating flavonoid and an effective amount of a hydrogen peroxide scavenger selected from the group consisting of catalase, superoxide dismutase and glutathione peroxidase. Claim 9 embodies the method of claim 8 wherein said hydrogen peroxide scavenger catalyzes the decomposition of hydrogen peroxide. Claim 11

embodies the method of claim 8 wherein the administration of said NK cell activating flavonoid and said hydrogen peroxide scavenger is performed simultaneously.

The abstract of Tatsuo (JP 59059628) teaches an antitumor formulation comprising kaempferol and catalase. The abstract of Tatsuo (JP 59059627) teaches an antitumor formulation comprising kaempferol and peroxidase. It would have been prima facie obvious at the time the claimed invention was made to administer the compositions of either Tatsuo (JP 59059628) or Tatsuo (JP 59059627) to a subject having a tumor. One of skill in the art would have been motivated to do so by the abstracts which describe the formulations as having antitumor agents. The abstract do not specifically state that kaempferol activates NK cells, however, kaempferol is a flavonoid compound and in combination with catalase or peroxidase exerts an antitumor effect which is the same as that claimed. The Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the product of the instant method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the product of the instant method is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claims 1-3, 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hellstrand et al (WO 91/04037) in view of the abstract of Oleksowicz et al (Am J Ther. 1994 Aug;1(2):107-115.)

Claim 1 is drawn in part to a method of inhibiting tumor growth in a subject comprising administering to a subject with a neoplastic disease in need thereof an effective amount of a NK-cell activating cytokine and an effective amount of a compound which inhibits the production or release of hydrogen peroxide selected from the group consisting of histamine, other H2 receptor agonists and serotonin, and wherein the NK activating cytokine is not IL-2 or IFN alpha. Claim 2 embodies the method of claim 1 wherein the administration of said NK activating cytokine and said compounds is performed simultaneously. Claim 3 embodies the method of claim 1 wherein the administration of said compound is performed within 24 hours of the administration of said

NK cell activating cytokine. Claim 6 embodies the method of claim 1 wherein said histamine, other H2 receptor agonist or serotonin is administered parentally to said subject.

Hellstrand et al teach a method of treating a neoplastic disease in a subject comprising the administration of histamine or other H2 receptor agonist in combination with the administration of the cytokine Il-2 (page 7, lines 9-18). Hellstrand et al teach that the compounds can be administered in the same composition (page 6, lines 31-33) or in separate compositions within the same day (page 11, lines 19-21), thus fulfilling the specific embodiments of claims 2 and 3. Hellstrand et al teach that the amount of histamine is 0.1 to 10 mg/day (page 9, lines 9-13), thus fulfilling the specific embodiment of claim 6. Hellstrand et al teach the parenteral administration of the histamine and Il-2 (page 8, lines 7-8), which fulfills the specific embodiment of claim 7. Hellstrand et al do not teach a NK activating cytokine other than Il-2.

Oleksowicz et al teach that IL-12 has been shown to enhance the lytic activity of nonspecific NK/LAK cells and appears to be more efficient than IL-2 or IFN's in enhancing NK cytotoxicity.

It would have been prima facie obvious at the time the claimed invention was made, to substitute Il-2 for Il-2 in the method of treating tumor growth taught by Hellstrand et al. One of skill in the art would have been motivated to do so by the teachings of the abstract of Oleksowicz et al on the enhanced ability of Il-12 to stimulate NK cell cytotoxicity relative to Il-2.

All other rejections an objections as set forth or maintained in the prior office action are withdrawn in light of applicants amendments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
10/31/2005